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Probability distribution describing stage of viremia in animals entering quarantine

Some additional parameters associated with the duration of viremia are described in this section. Specifically, (1) the mathematical convention used to model how long infected animals have been viremic when they enter quarantine is described, and (2) the validity of this approach is demonstrated by using a simple mathematical model for the stage of viremia of animals entering quarantine. This represents a group of animals in which disease prevalence and incidence are constant.

Stage of viremia

When a sample is taken as a part of a survey or for selecting animals for export (such as a sample of animals entering quarantine), infected animals comprise subpopulations of animals infected at various times in the past. For a given distribution of duration of viremia that has a minimum (= j) and a maximum (= k) of viremia, viremic animals entering the quarantine facility will have been infected between j and k days before and will have been infected from j to k days at the time of entry. Even if an animal is tested and tests positive at the time of entry, an observer does not know long the animal has been viremic, only that it is or is not viremic. However, the stage of viremia (how long animal has been viremic) is a critical variable because the probability that an animal will be viremic at the conclusion of a quarantine period is directly related to the stage of viremia when it enters.

What distribution correctly describes the probability that a viremic animal has been viremic for x days? The distribution for stage of viremia specifies the probability an animal will remain viremic for a certain period of time and thus does not describe the distribution for stage of viremia in sampled animals because they became infected at many different times.

We wish to assess the probability that an animal is viremic after x days. The cumulative distribution, $F(x) = Pr(X < x)$, describes the probability an animal will remain viremic x days or less. A mathematical convention from reliability engineering, the exceedence distribution or $1 - F(x) = 1 - Pr(X < x) = Pr(X>x)$, expresses the probability that a random variable will exceed a certain value. When normalized to conform to the requirements of a probability mass or density function, this exceedence distribution provides precisely the information APHIS wishes to acquire.

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The validity of this hypothesis is demonstrated in the following example.

Hypothetical example: Distribution of stage of viremia among viremic animals

To validate the assertion that the normalized exceedence distribution properly models the distribution of stage of viremia, we engage in a simple "thought experiment" and generate a simple mathematical model to quantify this experiment.

Consider a population in which a certain portion of animals is infected with a disease. After some latent period following infection, the animals become viremic and remain viremic for varying lengths of time. Further let us assume that

1. the prevalence or proportion of the viremic population is constant over time;
2. the incidence or number of new cases is constant over time; and
3. all viremic-infected animals eventually revert to a non-viremic state.

Assumption 3 is a requirement for assumption 1 to flow from assumption 2. In such a population the number of animals becoming infected per time unit is constant, and the number of animals that becomes non-viremic is constant over time.

The distribution for the duration of viremia for the disease in our thought experiment is presented in Table 9 (see also Figure 3). The curves illustrating the cumulative and exceedence distributions are found in Figure 4.

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Table 9. Hypothetical Distribution for Duration of Viremia

Duration	Prob.	Pr(X<x)	Pr(X>=x)	Normalized Exceedence /1
1	0.1	0	1	0.3333
2	0.2	0.1	0.9	0.3
3	0.4	0.3	0.7	0.2333
4	0.2	0.7	0.3	0.1
5	0.1	0.9	0.1	0.0333
6	0	1	0	

The values for 1/ Pr(X>=x) are normalized so probabilities sum to 1.0.

We arbitrarily assume further that there is a 2-day lag from infection to the onset of viremia.

Figure 3. Hypothetical Distribution for Duration of Viremia After 2-Day Lag from Time of Infection

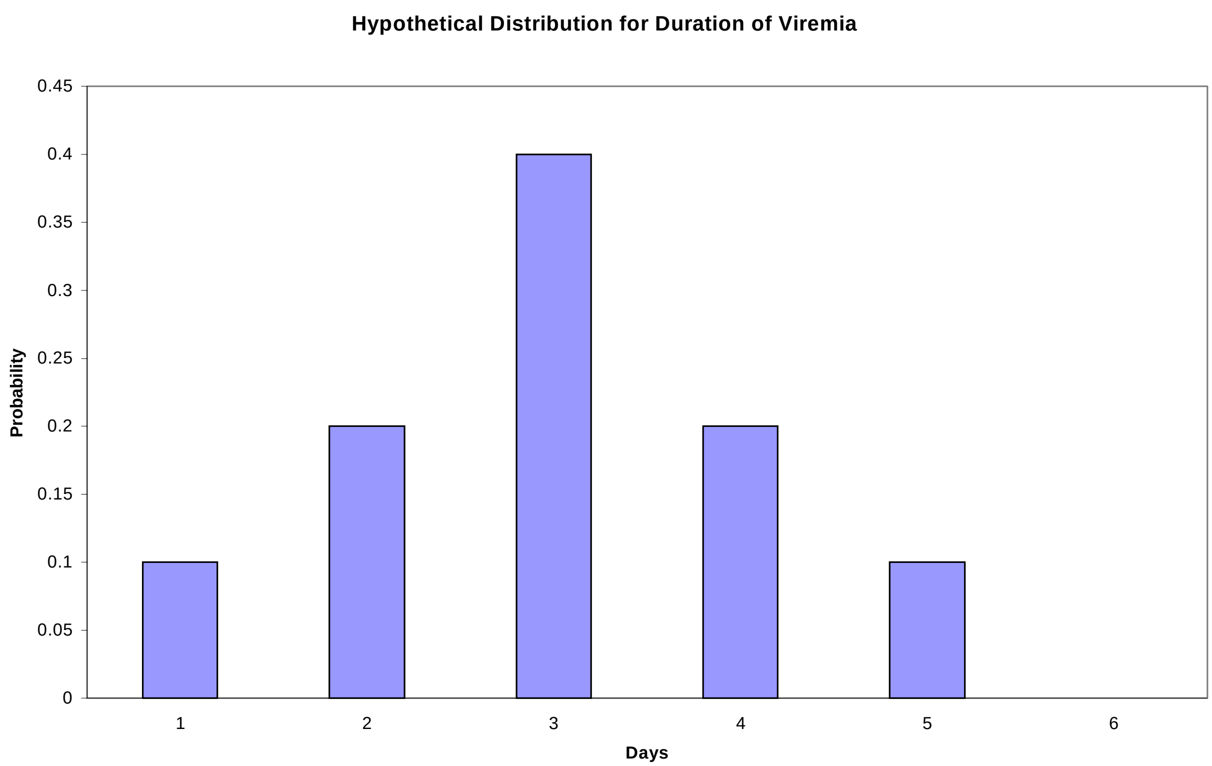

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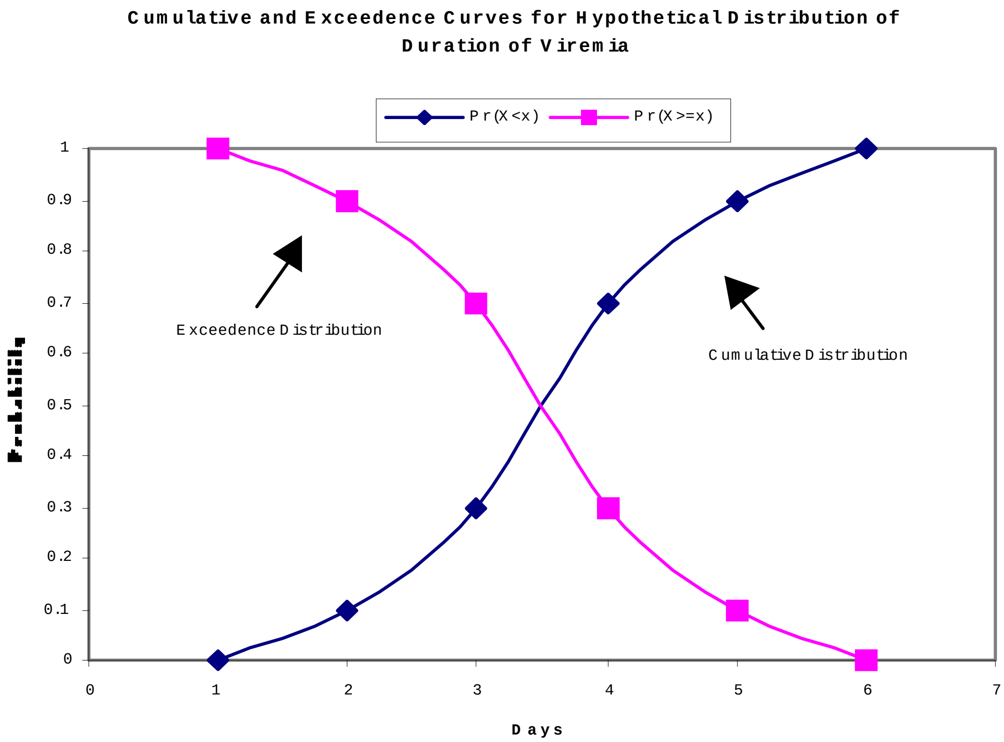
Figure 4. Cumulative and Exceedence Probability Curves for Duration of Viremia.



Note in Table 9 and Figure 4 that we altered the definition of the cumulative distribution. Typically the cumulative distribution is defined as

$$F(X) = Pr(X < x)$$

and the exceedence distribution is defined as

$$F(X) = 1 - Pr(X < x).$$

However, because we are interested in the probability that the stage of viremia is greater than or equal to a certain time period, we change the less than or equal to in the cumulative to a less than, thus changing the exceedence to a greater than or equal to as follows:

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Cumulative: $F(X) = Pr(X < x)$
Exceedence: $1 - F(X) = Pr(X > x)$.

Note in Table 9 that the probabilities for duration of viremia (column 2) sum to 1.0 whereas the exceedence and cumulative probabilities do not. To make our exceedence distribution conform to the mathematical requirements of a probability distribution, we normalize it (made the probabilities sum one), yielding the probabilities in the right column of Table 9.

Now let us envision the infection of animals over time as those developing viremia, and becoming non-viremic. Table 10 presents a time-probability matrix that shows the probability that an animal infected on any day between 1 and 15 (right-hand column) will be viremic on a given day after that (top row of table).

Table 10. Time-Probabiity Matrix for Probability Animal is Viremic Subsequent to Infection

	Day														
Day Infected	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
	Probabilty Viremic														
0		1	0.9	0.7	0.3	0.1									
1			1	0.9	0.7	0.3	0.1								
2				1	0.9	0.7	0.3	0.1							
3					1	0.9	0.7	0.3	0.1						
4						1	0.9	0.7	0.3	0.1					
5							1	0.9	0.7	0.3	0.1				
6								1	0.9	0.7	0.3	0.1			
7									1	0.9	0.7	0.3	0.1		
8										1	0.9	0.7	0.3	0.1	
9											1	0.9	0.7	0.3	0.1
10												1	0.9	0.7	0.3

$$1.0 - 0.1 = 0.9$$

In Table 10, the entries for a row show the probability an animal is viremic on the day indicated by the column heading in the table: at day 3 (2 days after infection) 100 percent of the animals are viremic; thus, the probability that an animal is viremic is 1.0. On day 4, the probability an animal infected on day 1 is viremic is computed by subtracting the probability an animal remains viremic only one day (0.1) from the probability the animal was viremic on day 3 (1.0):

$$1.0 - 0.1 = 0.9$$

We extend our illustration similarly for days 5, 6, and 7. Note the vector of non-zero probabilities in any row is equal to the probabilities in the exceedence distribution
(e.g., $Pr(X > x)$ in Table 9. This pattern is repeated each day as new animals become infected.

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To determine the probability distribution for the stage of viremia, we assume that 100 animals become infected each day. Given the probability that an animal is viremic j days post-infection is p, the expected number of animals infected on that day is np, where n = number of animals infected on the given day. Thus if 100 animals (n) are infected on day 3 and the probability that an animal is viremic on day 6 = p = 0.9, the mean or expected number of animals viremic on that day = np = 100 x 0.9 = 90.

Table 11. Expected Number of Viremic Animals Subsequent to Infection, By Day

	No.	Day														
Day Infected	Infected	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
		Expected Number of Animals Viremic														
0	100	0	100	90	70	30	10	0	0	0	0	0	0	0	0	0
1	100	0	0	100	90	70	30	10	0	0	0	0	0	0	0	0
2	100	0	0	0	100	90	70	30	10	0	0	0	0	0	0	0
3	100	0	0	0	0	100	90	70	30	10	0	0	0	0	0	0
4	100	0	0	0	0	0	100	90	70	30	10	0	0	0	0	0
5	100	0	0	0	0	0	0	100	90	70	30	10	0	0	0	0
6	100	0	0	0	0	0	0	0	100	90	70	30	10	0	0	0
7	100	0	0	0	0	0	0	0	0	100	90	70	30	10	0	0
8	100	0	0	0	0	0	0	0	0	0	100	90	70	30	10	0
9	100	0	0	0	0	0	0	0	0	0	0	100	90	70	30	10
10	100	0	0	0	0	0	0	0	0	0	0	0	100	90	70	30
Total Viremic Animals		0	100	190	260	290	300	300	300	300	300	300	300	200	110	40

We now compute the number of animals viremic from infections starting on days 1 through 10, maintaining the assumption that 100 animals are infected daily, by multiplying the matrix in Table 10 by 100, resulting in the number of viremic animals present each day (Table 11).

Taking a day for which our model shows that steady state conditions prevail, when the number of viremic animals is constant over time (e.g. = 300) and analyzing the composition of the viremic animals by stage of viremia allows us to compute the appropriate probability distribution expressed as relative frequency (Table 12).

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Table 12. Composition of Viremic Animal Population by Stage of Viremia

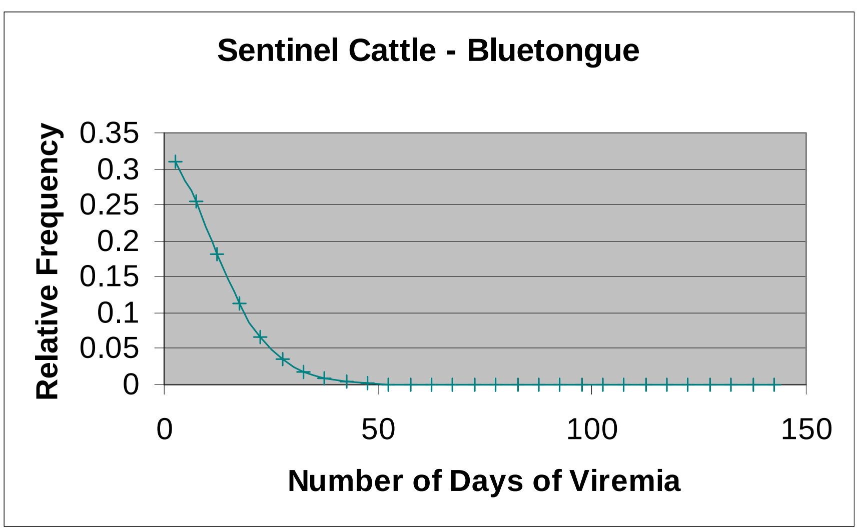
Composition of Viremic Animals on Day 7

Day Inf.	*Age of Viremia*	*No. Viremic*	*Relative Freq.*
5	1	100	0.333
4	2	90	0.300
3	3	70	0.233
2	4	30	0.100
1	5	10	0.033
Total		300	1.00

Note that the relative frequency or probability of age of viremia of Table 12 is identical to the normalized exceedence distribution shown in Table 9.

On the basis of the foregoing discussion, the descending cumulative distribution of values in Table 12 (exceedence distribution) is shown in Figure 5 and is used to estimate the number of days that an animal has been viremic, given that the animal is viremic when entering the quarantine facility.

Figure 5. Cumulative Distribution of Values in Table 12



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Although the distribution in Figure 5, is hypothetical, it may be used to illustrate the way in which p_3 is estimated. For this illustration, let us assume that the total time from onset of infection until entry into the U.S. (T4) is 25 days. In this illustration, p_3 corresponds to the y-axis value corresponding to 25 days on the x-axis. The value of p_3 for this illustration is approximately 0.06. For simplicity, individual values of p_3 generated from AQIS's data (reference page 10 of the assessment) are not reported.